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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,374	06/08/2001	Jeffrey C. Rapp	AVI-007N	2448

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AVIGENICS, INC.
111 RIVERBEND ROAD
ATHENS, GA 30605

EXAMINER	
TON, THAIAN N	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,374	RAPP, JEFFREY C.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9-29 and 62-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9-29 and 62-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/10/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-0-2

DETAILED ACTION

Applicants' Amendment, filed 2/22/05, has been entered. Claims 71-72 are currently amended. Claims 1-5, 7, 9-29, 62-73 are pending. Claim 73 has been withdrawn as election by original presentation, as stated in the Office action mailed on 6/29/04. Claims 1-5, 7, 9-29, 62-73 are under current examination.

The Examiner addresses Applicants' Remarks, presented in the amendment dated April 8, 2004 in this Office action.

Election/Restrictions

Upon further consideration, the Restriction Requirement mailed on 6/29/04, is withdrawn. The instantly pending claims are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-29, 62 and 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that the instant case is not analogous to the case law cited by the Examiner, because specific amino acids and/or nucleotide sequences were unknown at issue, and these cases were directed to compositions. Applicants argue that the instant claims are directed to methods of producing compositions, and that many sequences for immunoglobulin polypeptides, and their corresponding nucleotide sequences were readily available to the skilled practitioner at the time of filing, and there is no need to isolate or characterize nucleotide sequences or amino acid sequences, to practice the claimed invention. Applicants point to WO 01/14424 which includes the nucleotide sequence of human CTLA4 antibodies, and is incorporated in the present application. The instant claims are directed to the production of immunoglobulins or antibodies, wherein these methods may be applied to nucleotide sequences which encode immunoglobulins or antibodies known at the time of filing. Thus, Applicants conclude that the written description requirement is fulfilled. See p. 9 of Applicants' Remarks, dated 4/8/04.

This is not persuasive. The production of the heterologous antibody, as instantly claimed, requires nucleotide sequences that produce an immunoglobulin sequence that forms an antibody that selectively binds to an antigen or an immunoglobulin polypeptide. The specification fails to describe nucleotide sequences that can produce a polypeptide that can bind selectively to any antigen/immunoglobulin polypeptide, as broadly claimed, with particularity to indicate that Applicants had possession of the claimed invention. The claimed

invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art **as of Applicants effective filing date**. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998).

The specification teaches the generation of separate vectors containing cDNA coding for either the heavy or light chain of human monoclonal antibody against CTLA-4 to produce antibodies [see Example 1]. The specification further teaches the transfection of cultured chicken whole embryo fibroblasts with the pCMV-L-IRES-H plasmid encoding the CTLA-4 human monoclonal antibody [see Example 3]. The specification further teaches the production of the human monoclonal antibody CTLA-4 in chick serum by sperm-mediated transgenesis [Example 4]. Thus, the specification only provides adequate written description for the claimed invention with regard to the human monoclonal CTLA-4 antibody.

In the instant case, the claimed embodiment of a nucleotide sequence that produces an immunoglobulin polypeptide that forms an antibody that selectively binds to an antigen or an immunoglobulin polypeptide lacks a written description. The specification fails to describe what nucleotide sequences fall into this genus

when expressed and used as claimed. The skilled artisan cannot envision the detailed chemical structure of all such nucleotide sequences, and therefore conception is *not* achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, because only the human CTLA-4 cDNA was described, it is the only nucleotide sequence meets the written description provision of 35 U.S.C. § 112.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4-9, 11, 12, 14-17, 20-29, 62 and 63 are rejected under 35 U.S.C. 102(a) as being anticipated by Ditullio *et al.* [cited in the Office action mailed 10/22/03]. This rejection is maintained for reasons of record advanced on pages 5-8 of the Office action mailed 10/22/03.

Applicants argue that Dituillio does not disclose or even suggest the claimed invention because they teach introduction of a nucleic acid into an avian blastodermal cells, which is not claimed in the instant invention. See p. 10, 2nd ¶ of the Response filed 4/8/04.

This is not persuasive. A blastodermal cell is a cell that is formed after the fertilization of the ovum, and the maturation of the ovum. See p. 6, lines 19-25 of Ditullio. The instant claims are directed to various cell types, including embryonic, oviduct or ovum. Thus, a blastodermal cell, as taught by Ditullio would, at the very least, be considered an embryonic cell. Furthermore, it results from an ovum and is

generated from the oviduct, and thus, would also be considered these cell types. Accordingly, it is maintained that Ditullio anticipate the claimed invention.

Claim 73 is rejected under 35 U.S.C. 102(b) as being anticipated by Heinzel *et al.* [**Infection & Immunity**, 67(12):6454-6460 (1999)].

The claim is drawn to an antibody specific for CTLA4 produced according to the method of 64. Thus, the claim is a product by process claim. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as

or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Heinzel teach anti-CTLA4 antibodies. See Abstract and p. 6455, Materials and Methods, Reagents, which teach hybridoma cells producing the anti-CTLA4 monoclonal antibody. Accordingly, they anticipate the claim.

Claim 73 is rejected under 35 U.S.C. 102(e) as being anticipated by Carreno *et al.* [**Pub. No. US 2002/0039581 A1**, published April 4, 2002, filed Jan. 26, 2001].

The claim is a product-by-process claim (see above). Carreno teach the production of CTLA4 antibodies, and specifically those that react to human CTLA4. See p. 1, paragraphs 6-9. Accordingly, they anticipate the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of claims 1, 3, 10, 13 under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* when taken with Michael *et al.* is maintained for reasons of record.

Applicants argue that the Examiner states that it would have been obvious for one of skill in the art to extend the teaching of Michael to expressin an avian cell, constructs of the present invention, because the cytomegalovirus promoter is well-characterized and well-known, and that the Examiner does not point to a source or provide an explanation where the motivation to combine the references comes from in the knowledge generally available to the skilled practitioner, and thus, the rejection should be withdrawn.

Applicants' arguments are not persuasive. Establishment of a *prima facie* case of obviousness, there must be some suggestion, either in the references or in the knowledge generally available in the art, to modify the references, or combine the teachings. See also, MPEP §2142. Thus, the Examiner, in the prior Office action (mailed 10/22/03) establishes that it is well-known in the art to use the CMV promoter because it is well-known, well-characterized and that such a promoter would allow for optimal levels and patterns of gene expression, that, utilizing an IRES element, would facilitate expression of multiple genes, and that viral transduction is an efficient way to deliver a construct of interest to a cell.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 64-73 rejected under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* when taken with Ling *et al.* [**Genomics**, 60:341-355 (1999)] and Najafian *et al.* [Exp. Opin. Invest. Drugs. 9(9): 2147-2157 (2000)].

Ditullio teach methods of generating transgenic avian. In particular, they teach the introduction of a nucleic acid molecule into the genome of an avian aspecies by contacting *in vivo* a blastodermal cell of a fertilized hard shelled egg [see p. 1-2]. The avian species can be, for example, a chicken [see p. 2, lines 9-12]. DiTullio teach that the nucleic acid can contain a sequence encoding an antibody or fragment thereof, for example, a monoclonal antibody, or a chimeric molecule [*e.g.,* containing antibody portions of both murine and human origin] [see p. 2, lines 22-28]. Ditullio discuss the transcriptional regulatory elements that are contained in the nucleic acid construct, such as initiation signals, enhancers, promoters, which induce or control the transcription of protein coding sequences to which they are operably linked [see p. 3, lines 1-5]. For example, the promoter may be constitutive or inducible, and may be tissue-specific, inducible by external signals or within an intron [see p. 3, lines 12-15]. Ditullio teach that the chicken lysozyme or ovalbumin promoter may be used with the described transgene construct [see p. 3, lines 15-17]. In particular, the invention includes a transgene expression cassette in which the heavy and light chain coding regions of an antibody are ligated together, each under the direction of its own promoter operably linked to a matrix attachment region [see p. 3, lines 24-26]. Ditullio that the avian cell can be targeted either *in vitro* or *in*

vivo [see pp. 7-10]. In particular, the cells of the blastoderm can be accessed by cutting or drilling a small hole in the eggshell and directly infusing the DNA into the blastoderm [see p. 7].

Ditullio do not specifically teach producing an antibody specific for CTLA4. However, prior to the time the claimed invention was made, Ling teach the sequence of human CTLA4, including its alignment with the mouse CTLA4 sequence. See Figure 3. Ling teach that CTLA4 has been correlated with specific diseases (see p. 341, 2nd column). Najarfian provide the requisite motivation for the production of CTLA4 antibodies, as instantly contemplated. They teach that CTLA-4 is only expressed on activated T-cells, and that CTLA-4 negative signaling pathways maybe required for the induction of acquired tolerance. See p. 2148, 2nd column, Introduction.

Accordingly, in view of the combined teachings, it would have been obvious for the skilled artisan to modify the technique of producing antibodies in avian species, as taught by Ditullio, utilizing a construct encoding CTLA-4, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make such a modification, as the art recognizes the importance of suppressing CTLA-4 to generate acquired tolerance, for example.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tnt
Thaian N. Ton
Patent Examiner
Group 1632

Joe Woitach
AU1632